IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of: Tracey, *et al.*	)	Examiner: L. Royds
Patent No: 7,273,872	)	Art Unit: 1614
Issued: September 25, 2007	)	Conf. No.: 8405
For: Inhibition of Inflammation Using Alpha-7 Receptor-binding Cholinergic Agonists	)	

NOTIFICATION OF EUROPEAN OPPOSITION PROCEEDING

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

While prosecution is closed with respect to the U.S. Application Serial No. 10/729,427 (now U.S. Patent No. 7,273,872), Applicants respectfully request that the European opposition proceeding of corresponding EP 1 581 233 be made of official record in the file history of the instant patent. Thus, Applicants submit herewith a copy of the resulting claims as evidence of the opposition proceeding.

If the Office has any questions regarding this submission, the Office is urged to contact the undersigned.

Respectfully submitted,

Date: December 10, 2010

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Europäisches Patentamt
European Patent Office
Office européen des brevets

Anmeldenummer	Application No.	Numéro de la demande:
	03796701.5	

INFORMATION

Die mündliche Verhandlung am:	The oral proceedings of: 18.11.10	La procédure orale du:
hat ergeben:	resulted in:	fut conclue comme suit:
☐ Das europäische Patent wird widerrufen da wenigstens ein Einspruchsgrund der Aufrechterhaltung des europäischen Patents entgegensteht (Art. 101(2) EPÜ).	The European patent is revoked because at least one ground for opposition prejudices the maintenance of the European patent (Art. 101(2) EPC)	Le brevet européen est révoqué car au moins un motif d'opposition s'oppose au maintien du brevet européen (art. 101(2) CBE).
☐ Das europäische Patent wird widerrufen, da unter Berücksichtigung der vom Patentinhaber im Einspruchsverfahren vorgenommenen Änderungen das europäische Patent und die Erfindung, die es zum Gegenstand hat, den Erfordernissen des EPÜ nicht genügen (Art. 101 (3) b) EPÜ).	The European patent is revoked because, account being taken of the amendments made by the patent proprietor during opposition proceedings, the patent and the invention to which it relates were found not to meet the requirements of the EPC (Art. 101(3)(b) EPC).	Le brevet européen est révoqué car il a été établi que, compte tenu des modifications apportées par le titulaire du brevet au cours de la procédure d'opposition, le brevet et l'invention qui en fait l'objet ne satisfont pas aux exigences de la Convention sur le brevet européen (art. 101(3)(b) CBE).
☐ Der Einspruch wird/Die Einsprüche werden zurückgewiesen (Art. 101(2) EPÜ).	The opposition(s) is/are rejected (Art. 101(2) EPC).	L'opposition est/Les oppositions sont rejetée(s) (art. 101(2) CBE).
☒ Es wird festgestellt, dass unter Berücksichtigung der vom Patentinhaber im Einspruchsverfahren vorgenommenen Änderungen das Patent und die Erfindung, die es zum Gegenstand hat, den Erfordernissen des Europäischen Patentübereinkommens genügen (Art. 101(3)(a) EPÜ).	Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of European Patent Convention (Art. 101(3)(a) EPC)	Il est établi que, compte tenu des modifications apportées par le titulaire du brevet au cours de la procédure d'opposition, le brevet et l'invention qui en fait l'objet satisfont aux exigences de la Convention sur le brevet européen (art. 101(3)(a) CBE).
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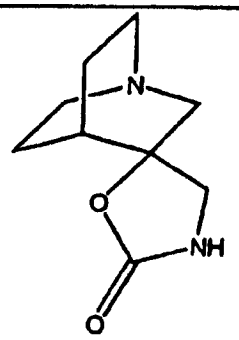
NB: Dieses Formblatt ist nur als Information zu sehen. Die schriftliche Entscheidung hat Vorrang.
This form is provided for the sake of information only. The written decision prevails.
Le présent formulaire n'a qu'une valeur informative. La décision écrite prévaut.

Aux. Request I



(-)-spiro-1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one

(VII)

[0100] Murine RAW 264.7 macrophage-like cells (American Type Tissue Culture Collection, Rockville, Md., USA) were grown as described above in Example 3. The cells were treated with (-)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one] (Compound (VII)) at 0, 0.01, 0.1, 1, 10 and 100 uM. Five minutes after the addition of Compound (VII), the cells were treated with LPS (500 ng/ml). TNF-α was measured by ELISA as described above.

[0101] The results are shown in FIG. 11, which demonstrate that the higher concentrations of Compound (VII) inhibit TNF-α release from RAW 264.7 cells. TNF-α release was decreased by more than four times in cells treated with 100 uM Compound (VII) compared to control cells.

[0102] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantages attained.

Claims

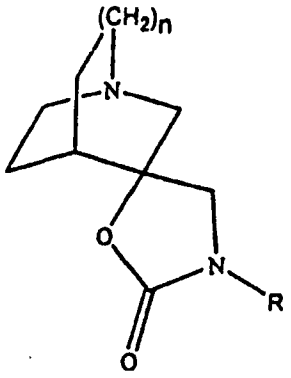
1. Use of a cholinergic agonist selective for an α7 nicotinic receptor for the preparation of a medicament for treating an inflammatory condition:

   wherein said condition is selected from appendicitis, peptic, gastric and duodenal ulcers, peritonitis, pancreatitis, epiglottitis, achalasia, cholangitis, cholecystitis, hepatitis, Whipple's disease, asthma, allergy, anaphylactic shock, immune complex disease, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, hyperpyrexia, eosinophilic granuloma, granulomatosis, sarcoidosis, septic abortion, epididymitis, vaginitis, prostatitis, urethritis, bronchitis, emphysema, rhinitis, cystic fibrosis, pneumonitis, pneumoultramicroscopic silicovolcanoconiosis, alveolitis, bronchiolitis, pharyngitis, pleurisy, sinusitis, influenza, respiratory syncytial virus infection, herpes infection, HIV infection, hepatitis B virus infection, hepatitis C virus infection, disseminated bacteremia, Dengue fever, candidiasis, malaria, filariasis, amebiasis, hydatid cysts, burns, vasulitis, anglitis, endocarditis, arteritis, atherosclerosis, thrombophlebitis, pericarditis, myocarditis, periarteritis nodosa, rheumatic fever, coeliac disease, congestive heart failure, adult respiratory distress syndrome, chronic obstructive pulmonary disease, meningitis, encephalitis, neuritis, neuralgia, spinal cord injury, paralysis, uveitis, arthritides, arthralgias, osteomyelitis, fasciitis, Paget's disease, gout, periodontal disease, rheumatoid arthritis, synovitis, myasthenia gravis, thryoiditis, systemic lupus erythematosus, Goodpasture's syndrome, Behcets's syndrome, allograft rejection, graft-versus-host disease, ankylosing spondylitis, Berger's disease, Retier's syndrome, and Hodgkins disease.

2. The use of claim 1, wherein the cholinergic agonist is selected from a quaternary analog of cocaine; (1-aza-bicyclo [2.2.2]oct-3-yl)-carbamic acid 1-(2-fluorophenyl)-ethyl ester; a compound of formula I:

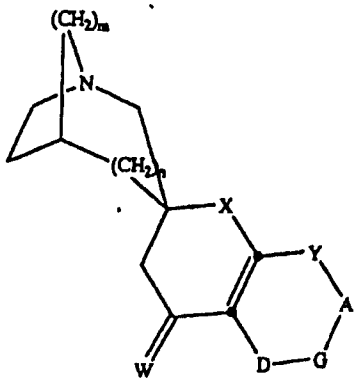
(in an amount sufficient to decrease the amount of a proinflammatory cytokine that is released from a macrophage)

T. Friede
18.11.2010



I

wherein, R represents hydrogen or methyl, and
n represents 0 or 1; a pharmaceutically acceptable salt of a compound of formula I; a compound of formula II:

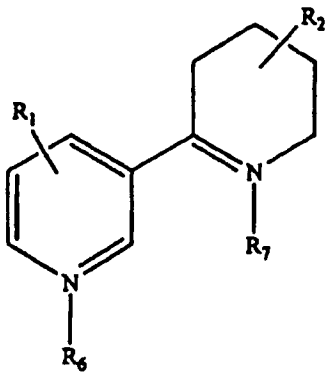


II

wherein:

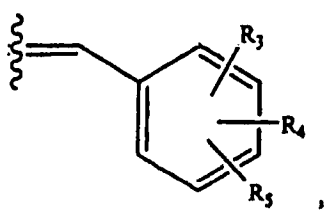
m is 1 or 2,
n is 0 or 1,
Y is CH, N or NO,
X is oxygen or sulfur,
W is oxygen, H_2 or F_2,
A is N or C(R^2),
G is N or C(R^3),
D is N or C(R^4),
with the proviso that no more than one of A, G and D is nitrogen but at least one of Y, A, G and D is nitrogen or NO,
R^1 is hydrogen or C_1-C_4 alkyl,
R^2, R^3 and R^4 are independently hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, heteroaryl, OH, OC_1-C_4 alkyl, CO_2R_1, -CN, -NO_2, -NR_5R_6, - CF_3 or -OSO_2CF_3, or R^2 and R^3, R^3 and R^4, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing between zero and two nitrogen atoms, and substituted with one to two of the following substitutents: independently hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, heteroaryl, OH, OC_1-C_4 alkyl, CO_2R^1, -CN, -NO_2, -NR^5R^6, -CF_3 or -OSO_2CF_3,
R^5 and R^6 are independently hydrogen, C_1-C_4 alkyl, C(O)R^7, C(O)NHR^8, C(O)OR^9, SO_2R^{10} or may together

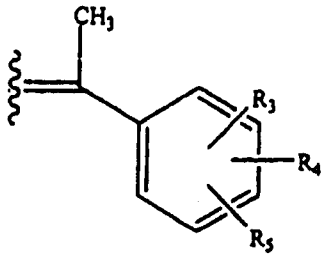
be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11}, or a bond,
j is 2 to 7,
k is 0 to 2,
R^7, R^8, R^9, R^{10} and R^{11} are independently C_1-C_4 alkyl, aryl, or heteroaryl, or an enantiomer thereof; a pharmaceutically acceptable salt of a compound of formula II; a compound of formula III:

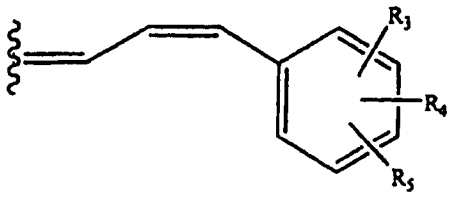


III

wherein R_1, R_6 and R_7 are hydrogen or C_1-C_4 alkyl, and R_2 is selected from a group of

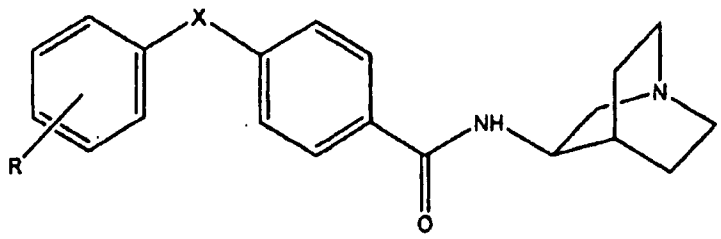






and

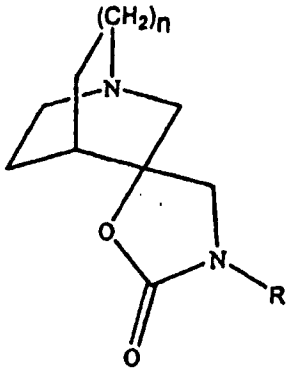
wherein, R_3, R_4 and R_5 are selected from hydrogen, C_1-C_4 alkyl optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, C_1-C_8 alkoxy optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, carboalkoxy having 1 to 4 carbons in the alkoxy, amino, amido having 1 to 4 carbons in the acyl, cyano, and N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, halo, hydroxyl or nitro; and a compound of formula IV:



IV

wherein X is O or S, and R is selected from the group consisting of H, OR_1, $NHC(O)R_1$, and a halogen, wherein R_1 is a C_1-C_4 alkyl.

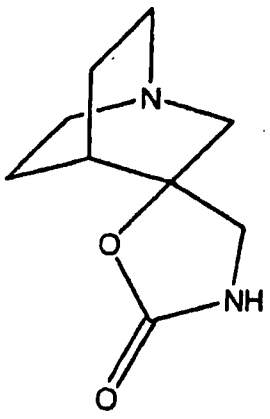
3. The use of claim 1, wherein the cholinergic agonist is a compound of formula I:



I

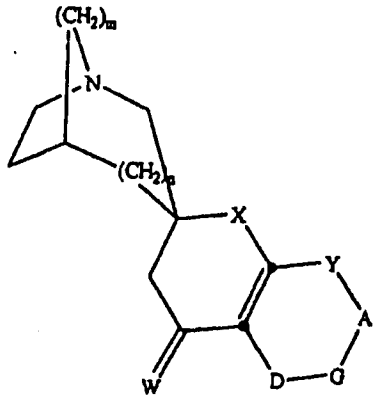
wherein, R represents hydrogen or methyl, and
n represents 0 or 1;
or a pharmaceutically acceptable salt thereof.

4. The use of claim 3, wherein the cholinergic agonist is (-)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one]



(VII).

5. The use of claim 1, wherein the cholinergic agonist is a compound of formula II:



II

wherein:

m is 1 or 2;
n is 0 or 1;
Y is CH, N or NO;
X is oxygen or sulfur;
W is oxygen, H_2 or F_2;
A is N or C(R^2);
G is N or C(R^3);
D is N or C(R^4);
with the proviso that no more than one of A, G and D is nitrogen but at least one of Y, A, G and D is nitrogen or NO;
R^1 is hydrogen or C_1-C_4 alkyl;
R^2, R^3 and R^4 are independently hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, heteroaryl, OH, OC_1-C_4 alkyl, CO_2R_1, -CN, $-NO_2$, $-NR_5R_6$, $-CF_3$ or $-OSO_2CF_3$, or R^2 and R^3, R^3 and R^4, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing between zero and two nitrogen atoms, and substituted with one to two of the following substitutents:

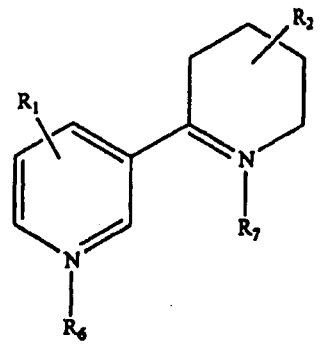
independently hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, heteroaryl, OH, OC_1-C_4 alkyl, CO_2R^1, -CN, $-NO_2$, $-NR^5R^6$, $-CF_3$ or $-OSO_2CF_3$;
R^5 and R^6 are independently hydrogen, C_1-C_4 alkyl, $C(O)R^7$, $C(O)NHR^8$, $C(O)OR^9$, SO_2R^{10} or may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11}, or a bond;
j is 2 to 7;
k is 0 to 2;
R^7, R^8, R^9, R^{10} and R^{11} are independently C_1-C_4 alkyl, aryl, or heteroaryl,
or an enantiomer thereof,

or a pharmaceutically acceptable salts thereof.

6. The use of claim 5, wherein the cholinergic agonist is a compound of formula II wherein m is 1; n is 0; p is 0; x is oxygen; A is $C(R^2)$; G is $C(R^3)$; and D is $C(R^4)$.

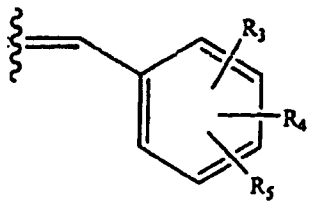
7. The use of claim 6, wherein the cholinergic agonist is 5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridin].

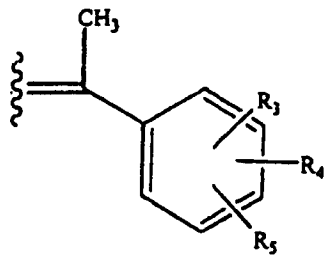
8. The use of claim 1, wherein the cholinergic agonist is a compound of formula III:

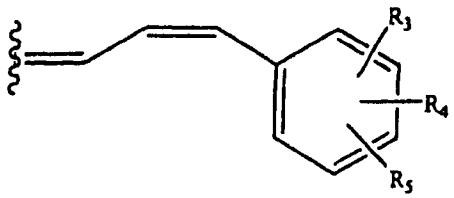


(III)

wherein R_1, R_6 and R_7 are hydrogen or C_1-C_4 alkyl; and R_2 is selected from a group of







and

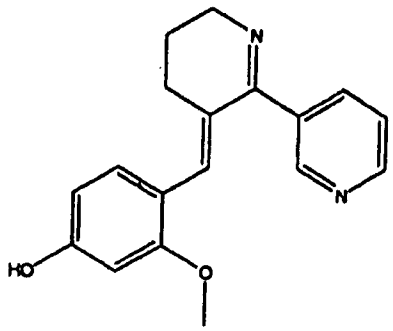
wheren, R_3, R_4 and R_5 are selected from hydrogen, C_1-C_4 alkyl optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, C_1-C_6 alkoxy optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, carboalkoxy having 1 to 4 carbons in the alkoxy, amino, amido having 1 to 4 carbons in the acyl, cyano, and N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, halo, hydroxyl or nitro.

9. The use of claim 8, wherein the cholinergic agonist is a compound of formula III, wherein R_2 is attached to the 3-position of the tetrahydropyridine ring, and further wherein R_3, which is attached to the 4- or the 2- position of the phenyl ring, is selected from the group consisting of amino, hydroxyl, chloro, cyano, dimethylamino, methyl, methoxy, acetylamino, acetoxy, and nitro.

10. The use of claim 8, wherein the cholinergic agonist is a compound selected from formula III, wherein R_3 is hydroxyl, and wherein R_1, R_4, and R_5 are hydrogen; formula III, wherein R_3 is acetylamino and wherein R_1, R_4, and R_5 are hydrogen; formula III, wherein R_3 is acetoxy and wherein R_1, R_4, and R_5 are hydrogen; formula III, wherein R_3 is methoxy, and wherein R_1, R_4, and R_5 are hydrogen; formula III, wherein R_3 is methoxy and wherein R_1 and R_4 are hydrogen, and further wherein R_3 is attached to the 2-position of the phenyl ring, and R_5, which is attached to the 4-position of the phenyl ring, is methoxy or hydroxy.

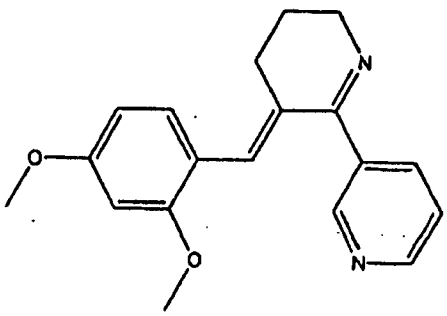
11. The use of claim 8, wherein the cholinergic agonist is is selected from 3-2,4-dimethoxybenzylidine anabaseine (DMXB-A), 3-(4-hydroxybenzylidene)anabaseine, 3-(4-methoxybenzylidene)anabaseine, 3-(4-aminobenzylidene) anabaseine, 3-(4-hyrdoxy-2-methoxybenzylidene)anabaseine, 3-(4-methoxy-2-hydroxybenzylidene)anabaseine, trans-3-cinnamylidene anabaseine, trans-3-(2-methoxy-cinnamylidene)anabaseine and trans-3-(4-methoxycinnamylidene)anabaseine.

12. The use of claim 8, wherein the cholinergic agonist is 3-(4-hydroxy-2-methoxybenzylidene)anabasine



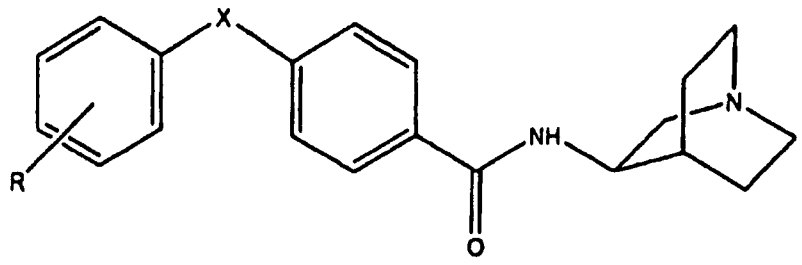
(VI).

13. The use of claim 8, wherein the cholinergic agonist is 3-(2,4-dimethoxybenzylidene)anabaseine.



(V).

14. The use of claim 1, wherein the cholinergic agonist is a compound of formula IV:



IV

wherein X is O or S; and
R is selected from H, OR_1, $NHC(O)R_1$, and a halogen, wherein R_1 is a C_1-C_4 alkyl.

15. The use of claim 13, wherein the cholinergic agonist is selected from N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-hydroxyphenoxy)benzamide, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-acetamidophenoxy)benzamide, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(phenylsulfanyl)benzamide, and N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(3-chlorophenylsulphonyl)benzamide.

16. The use of claim 13, wherein the cholinergic agonist is N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(phenylsulfanyl)benzamide.

17. The use of claim 1, wherein the cholinergic agonist is cocaine methiodide.

18. The use of claim 1 wherein the condition is selected from appendicitis, peptic, gastric and duodenal ulcers, peritonitis, pancreatitis, hepatitis, asthma, allergy, anaphylactic shock, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, septic abortion, disseminated bacteremia, burns, coeliac disease, congestive heart failure, adult respiratory distress syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosis, spinal cord injury, paralysis, allograft rejection and graft-versus-host disease.

19. The use method of claim 1 wherein the condition selected from appendicitis, peptic, gastric or duodenal ulcers, peritonitis, pancreatitis, hepatitis, asthma, allergy, anaphylactic shock, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, septic abortion, disseminated bacteremia, burns, congestive heart failure, adult respiratory distress syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosis, spinal cord injury, paralysis, allograft rejection or graft-versus-host disease.

20. The use of Claim 1 wherein the condition is selected from peritonitis, pancreatitis, sepsis, endotoxic shock, adult respiratory distress syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosis, allograft rejection, asthma, graft-versus-host-disease, congestive heart failure and cystic fibrosis.

21. The use of claim 1, wherein the condition is selected from peritonitis, pancreatitis, sepsis, endotoxic shock, cachexia, adult respiratory distress syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosis, and allograft rejection.

22. The use of claim 1, wherein the condition is sepsis.

~~Patentansprüche~~

~~1. Verwendung eines cholinergen Agonisten, der selektiv für einen α7-Nicotinrezeptor ist, zur Herstellung eines Me~~